



Letter to the Editor

Schizophrenia aetiology: Do gene-environment interactions hold the key? Comment on Tandon et al.

1. Heritability is more than genetic main effects

Tandon and colleagues point out that while no genetic variation has been consistently associated with schizophrenia, there is more consistent evidence implicating a range of environmental factors. The authors cite heritability estimates in schizophrenia of around 80%, and interpret these as indicating that 80% of the liability to schizophrenia is genetic. Heritability estimates, however, are derived from genetic epidemiological studies that estimate simple genetic and simple environmental contributions to schizophrenia liability; unfortunately, these do not model the contribution of gene-environment interactions ($G \times E$), because researchers tend to not include direct measures of the environment in such studies, thus precluding the quantification of gene-environment interactions. Therefore, the heritability of schizophrenia may be 80%, but simulations show that gene-environment interactions may make up the bulk of this proportion (Van Os and Sham, 2003). While many thousands of studies have focused on the interpretation of heritability as indicating pure genetic effects, a small but growing number of studies have attempted to measure both genes and environments and conduct gene-environment interaction analyses.

2. Gene-environment interaction studies

Gene-environment interaction studies can be powerful, as they do not necessarily rely on direct molecular measures of genetic variation (Murray et al., 1986). Instead, they can model genetic contributions using a range of genetically sensitive adoption, twin or family designs, or use intermediate biological phenotypes previously linked to genetic risk (Van Os and Marcelis, 1998). Although Tandon and colleagues do not review

the evidence for gene-environment interaction, there is consistent, albeit preliminary, evidence for $G \times E$ from a range of studies using indirect measures of genetic risk, including, for example, four replications of gene-urbanicity interaction (review by van Os and Poulton, 2008). These important early findings are now being extended to studies using direct molecular genetic measures of genetic variation in schizophrenia and related mental disorders (Caspi et al., 2005; Nicodemus et al., in press; Stefanis et al., 2007). Given these promising developments, there is an urgent need for well-conducted, large-scale $G \times E$ studies.

3. Challenges facing $G \times E$ studies

Systematic attempts to identify gene-environment interaction cannot be equated with traditional molecular genetic studies with a few putative environmental variables thrown in. The study of $G \times E$ is a multidisciplinary exercise involving epidemiology, psychology, psychiatry, neuroimaging, pharmacology, biostatistics and genetics. The challenges to overcome in the years to come are numerous and will be briefly outlined here.

3.1. The environment

First, it is extremely difficult to measure and model environmental effects (Jones and Cannon, 1998). Epidemiological studies of environmental risks are prone to bias, confounding and reverse causality, and the genetic liability to schizophrenia may increase the risk of exposure to certain environments (genetic control of exposure to the environment) rather than be moderated by them (genetic control of sensitivity to the environment) (Collip et al., in press). Therefore, observational studies on environmental effects need to be complemented by experimental studies using placebo-controlled random assignment to environmental exposures which, in combination with genotyping, allow for experimental ecogenetic approaches (Henquet et al., 2006). The advent of

controlled experiments with virtual-reality environments may similarly represent an important asset for the study of environmental exposures (Freeman et al., 2003). Second, the environment can be conceptualized at many levels that may all be relevant to behavioural phenotypes associated with schizophrenia, varying from minor stressors in the flow of daily life as assessed by momentary assessment technologies (Myin-Germeys et al., 2001), to contextual effects of the wider social environment such as neighbourhoods or ethnic density (Boydell et al., 2001; Kirkbride et al., 2007). Third, some environmental risks such as “urbanicity” and “ethnicity” are proxies for as yet unidentified environmental or possibly even genetic factors (Pedersen and Mortensen, 2006; Selten et al., 2007). Fourth, “functional enviromics”, or the study of the mechanisms underlying environmental impact on the individual to increase the risk for psychopathology is still in its infant stages, with many hypotheses that remain to be tested. These include effects of the environment on (i) developmental programming and adult functional circuits of the brain, (ii) neuroendocrine and neurotransmitter functioning, (iii) patterns of interpersonal interactions that may shape risk for later psychopathology and (iv) affective and cognitive processing (Rutter, 2005). Conversely, hypotheses need to be tested about the neural mechanism by which genetic variation may increase susceptibility to environmental stressors. These mechanisms and their underlying pathophysiological pathways need to be clarified in order to develop *a priori* gene-environment interaction research paradigms. For example, it has been suggested that there may be synergistic effects of genes and environment in bringing about a “sensitization” (Featherstone et al., 2007) (Tenn et al., 2005) of mesolimbic dopamine neurotransmission (Collip et al., in press; Howes et al., 2004). This hypothesis is supported by (i) evidence quantifying the impact of stress and dopamine agonist drugs on mesolimbic dopamine release and subsequent sensitization (Arnsten and Goldman-Rakic, 1998; Boileau et al., 2006; Covington and Miczek, 2001) as well as stress-dopamine agonist cross-sensitization (Hamamura and Fibiger, 1993; Nikulina et al., 2004; Yui et al., 2000) and (ii) evidence indicating that genetic risk for schizophrenia is associated with underlying alterations in the dopamine system, including increased dopamine synaptic availability (Hirvonen et al., 2005), increased striatal dopamine synthesis (Huttunen et al., 2008; Meyer-Lindenberg et al., 2002) and increased dopamine reactivity to stress (Brunelin et al., 2008; Myin-Germeys et al., 2005). Thus, a case can be made for investigating genetic variation affecting dopamine neurotransmission in interaction with environmental risk factors such as stress and dopamine agonist drugs.

Molecular genetic and functional genomic studies focussing on genes associated with dopamine neurotransmission suggest that this gene group may be useful for G × E studies. For example, a recent large study focussing on gene-gene interaction (epistasis) and functional effects suggested that a network of interacting dopaminergic polymorphisms may increase risk for schizophrenia (Talkowski et al., 2008). Evidence for epistasis between genes impacting on dopamine signalling can be validated using a neural systems-level intermediate phenotype approach in humans. Recent work of this type, using a prefrontal function fMRI phenotype, similarly suggests epistasis between polymorphisms in genes that control dopamine signalling (Buckholtz et al., 2007; Meyer-Lindenberg et al., 2006). More specifically, there is evidence that schizophrenia may be characterised by a combination of prefrontal cortical dysfunction and sub-cortical dopaminergic disinhibition (Meyer-Lindenberg et al., 2002). Research has shown that the valine-allele carriers of a functional polymorphism in the catechol-O-methyltransferase gene (COMT Val¹⁵⁸Met), an important enzyme regulating prefrontal dopamine turnover, predicted increased dopamine synthesis in the midbrain, suggesting that this allele may increase the risk for schizophrenia in interaction with, for example, stress and dopamine agonist drugs (Meyer-Lindenberg et al., 2005). Several studies suggest that valine-allele carriers may indeed be more sensitive to the psychotogenic effects of drugs of abuse or stress (Caspi et al., 2005; Henquet et al., 2006; Stefanis et al., 2007).

3.2. Genes

Traditional genetic approaches in schizophrenia are increasingly challenged by new insights into the complexities of genomic architecture and genetic regulation (Pearson, 2006). For example, deletions, insertions, duplications and complex multi-site variants, referred to as copy number variations (CNVs), are found in all humans, are functionally significant and likely of considerable contribution to phenotypic variation (Redon et al., 2006). Indeed, there is recent evidence implicating CNVs in the aetiology of some cases of schizophrenia (Kirov et al., 2008; Walsh et al., in press) as well as evidence going back some years that deletions of 22q11 are associated with greatly increased risk of the disorder (Murphy et al., 1999). In addition, there is evidence that protein-coding exons from one part of the genome combine with exons from another part that can be hundreds of thousands of bases away, with several other ‘genes’ in between or even spilling over the boundaries of chromosomes, creating a continuum of

transcripts. Similarly, vast amounts of the RNA manufactured by the human genome do not code for proteins but are actively processing and carrying out instructions in the genome, complicating traditional models of inheritance. Of particular interest to the theme of $G \times E$ is the fact that environmental factors in schizophrenia may induce epigenetic changes resulting from promoter DNA methylation affecting gene expression in neural systems relevant for psychotic disorder. It has been argued that in particular the dopaminergic system may constitute a promising target for epigenetic study in the area of $G \times E$ (Abdolmaleky et al., 2008). The central reversible epigenetic modification to DNA is brought about by methylation of the cytosine residues that may be heritable and can alter gene expression and processes downstream thereof. These changes may interact with genetic vulnerability associated with genetic sequence variation. The consequence for the concept of gene-environment interaction is that one can envisage a process of environment \times epigenetic \times genetic interaction in schizophrenia (Fig. 1). For example, there is strong evidence from animal research that the prenatal and early postnatal psychosocial environment affects gene expression impacting on adult neurobiological systems implicated in psychiatric disorders (Jirtle and Skinner, 2007; Meaney and Szyf, 2005). These findings may shed light on the mechanism of similar prenatal and postnatal risk factors for schizophrenia such as replicated evidence of the effect of prenatal stress (Huttunen and Niskanen, 1978; Khashan et al., 2008; Van Os and Selten, 1998) and the possible association between early life stress and later psychotic

disorder (Morgan and Fisher, 2007). Thus, animal research has shown that early life stress affects adult environmental reactivity of the dopamine system (Hall et al., 1999) which may be mediated by epigenetic changes (Moffett et al., 2007). A recent human study reported that mesolimbic dopamine release in response to psychosocial stress depended on low early life maternal care (Pruessner et al., 2004). Thus, early environmental stressors may be associated with differential promoter DNA methylation patterns creating vulnerabilities for later environmental exposures, possibly in interaction with differential genetic sequence variation as discussed above. A comprehensive investigation of differential methylation-mediated epigenetic alterations, induced by environmental exposures is called for; a case for a plausible hypothesis-driven approach can be made for certain gene families and systems.

3.3. Phenotypes

The question implied by Tandon and colleagues is to what degree the changing DSM concepts of schizophrenia are helping rather than hampering research into the aetiology and epidemiology of schizophrenia (Al-lardyce et al., 2007). The study of molecular genetics and gene-environment interactions will likely catalyze a reappraisal of psychiatric nosology (Owen et al., 2007) and in order to elucidate converging pathways that are the site of biological synergism between genes and environments, a wide range of approaches employing intermediate (or endo-) phenotypes are necessary in, for

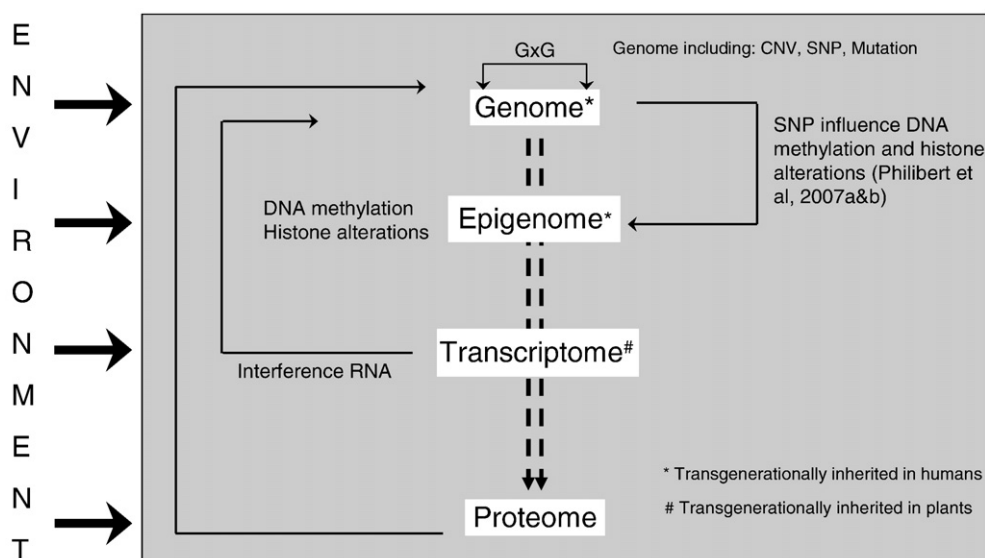


Fig. 1. Complexity of gene-environment interactions.

example, the domain of neural systems-level intermediate phenotypes (Barkus et al., 2007; Meyer-Lindenberg et al., 2006; Murray et al., 2008), cognition (Barnett et al., 2007a; Barnett et al., 2007b; Bombin et al., in press; Filbey et al., in press; Touloupoulou et al., 2007), neuroanatomy (Boos et al., 2007; Marcelis et al., 2003; van Haren et al., 2008), salience attribution (Jensen et al., 2008; Kapur, 2003), treatment response (Arranz and de Leon, 2007), measures of course and outcome (Verdoux et al., 1996), subclinical psychosis expression (Schurhoff et al., 2007; Schurhoff et al., 2003; Stefanis et al., 2004), neurotic symptoms (Zinkstok et al., 2008) and dynamic cerebral phenotypes in early onset groups (Arango et al., 2008).

3.4. Biostatistics

It is likely that mass genome-wide molecular genetic approaches, “enriched” with a few measures of “environmental” exposures will create invalid and confusing findings, largely because of the extent of multiple testing and the opportunities for post-hoc analyses afforded by such studies. It is of paramount importance to consider the study of $G \times E$ as a separate discipline, requiring a highly specialised and multidisciplinary approach taking both environment and genes seriously. A hypothesis-driven strategy focussing on pathways at which biological synergism between genetic and environmental mechanisms may take place, fed by information from functional enviromics and functional genomics pointing to promising neural systems and processes may constitute the most productive approach. In combination, this should enable a translational approach to systematically study the effect of environmental manipulations on neural systems linked to genetic risk for schizophrenia. However, even a hypothesis-driven approach is likely to face major challenges in the area of biostatistics. Even allowing for the major problem of how to bridge the gap between statistical interaction (statistical manipulations of data) and biological synergism (biological processes in nature), which currently cannot be estimated directly (Van Os and Sham, 2003), solutions to, for example, modelling multiple ambiguous haplotype \times environment interactions need to be developed further (Lake et al., 2003) and methods to increase power in $G \times E$ studies are urgently required (Boks et al., 2007).

4. Conclusion

In conclusion, the review by Tandon and colleagues is comprehensive and timely. Far from being a theo-

retical afterthought, the study of $G \times E$ now deserves center stage and multidisciplinary action, given the fact that a multitude of findings point to biological synergism that can now be elucidated given the right hypothesis-driven approach.

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